

**2. RESPONSE/REMARKS**

**2.1 STATUS OF THE CLAIMS**

*Claims 1-46, and 49-66 were pending at the time of the April 13 2006 Action and were examined on the merits.*

*Claims 34-46, 49-55, and 57-58 were withdrawn by the Examiner in the Action dated April 13, 2006.*

*Claims 20-23, 28-33 were canceled in Applicant's earlier response to the Action dated April 13, 2006, and those claims remain canceled herein.*

*Applicant has canceled claims 18, and 60-61 herein without prejudice and without disclaimer in response to the Notice of Non-Compliant Amendment dated January 19, 2007.*

*Applicant has amended claims 1, 10, 16, 17, 19, 24-27, 56, 59, and 62-66 herein.*

*Presently claims 1-17, 19, 24-27, 34-46, 49-59, and 62-66 are pending in the case.*

**2.2 APPLICANT NOTES THE FILING OF AN INFORMATION DISCLOSURE STATEMENT  
IN APPLICANT'S PRIOR RESPONSE DATED OCTOBER 13, 2006.**

*The Action of April 13, 2006 at page 4 objected to the Information Disclosure Statement as allegedly not complying with the requirements of 37 C. F. R. § 1.98(a)(2).*

In the response to Official Action dated October 13, 2006, Applicant respectfully traversed this rejection. However, in the interest of proceeding the case to allowance without further delay, Applicant filed concurrently with that amendment and response, a replacement IDS and a PTO Form SB/08a as part of their EFS-Web filing on October 13, 2006 that listed the references of record, and provided copies of each of the cited references. In the interest of brevity, Applicant has not reproduced that IDS herein, nor submitted a duplicate copy of the previous

IDS, since the Office did not indicate there were any deficiencies in its submission on the recent Notice of Non-Compliant Amendment. Should the Examiner require a new copy of the IDS, Applicant will be happy to provide one in response to such a request.

Applicant requests, therefore, that the Office consider the previously submitted IDS and that the Examiner initialize Form SB/08a as evidence of its consideration.

The substance of Applicant's October 13, 2006 Response to Official Action Dated April 13, 2006, as well as the remarks relating to the present Notice follow in Sections 2.3-2.9 below: With respect to the cancellation of claims 18, and 61-62 in the accompanying amendment, Applicant has modified the relevant sections of the response below to correctly reflect the canceled status of these 3 claims. Applicant respectfully requests that the present amendment be entered, and that the remarks and response herein be fully considered by the Office.

**2.3 THE OBJECTION TO CLAIMS 10, 17, 18, 25-27, 31 AND 32 IS OVERCOME.**

*The Action at pages 5-6 objected to claims 10, 17, 18, 25-27, 31, and 32 as allegedly containing informalities.*

Applicant appreciates the helpful suggestions of the Examiner in correcting these inadvertent typographical errors. Applicant also notes that claims 18, 31, and 32 have been canceled making their objection moot. Applicant now submits that these objections are overcome, and respectfully requests they be withdrawn.

**2.4 REJECTION OF CLAIMS UNDER 35 U. S. C. §101 IS RENDERED MOOT.**

*The Action at page 6 rejected claims 20, 22, 23, 28, 29, AND 33 under 35 U. S. C. § 101, allegedly because the claimed invention is directed to non-statutory subject matter.*

Applicant respectfully traverses; however, since these claims have been canceled, the rejection is moot. Applicant respectfully requests that the rejection be withdrawn.

**2.5 REJECTION OF CLAIMS UNDER 35 U. S. C. §112, 1<sup>ST</sup> PARAGRAPH, IS OVERCOME.**

*The Action at page 6-12 rejects claims 1-33, 56, 59-66 under 35 U. S. C. § 112, 1<sup>st</sup> paragraph, allegedly as failing to comply with the enablement requirement.*

Applicant respectfully traverses. However, in the interest of advancing certain claims of commercial importance to early allowance, Applicant has made the following amendments. Applicant notes that such amendments are in no way an indication of Applicant's acquiescence to the Examiner's rejection, and expressly reserves the right to re-file claims directed to the original scope of the amended claims.

Claims 1 and 63-65 have been amended by restricting the enucleated recipient cell to either an enucleated oocyte or an enucleated stem cell. These claims have been further restricted by including a proviso excluding the possibility of producing a primate embryo.

Claim 16 has been amended to recite a *non-primate* embryo and to the use of an enucleated recipient **oocyte**. Additional steps such as embryo activation, culturing to a suitable stage of development and transferring to a female surrogate have also been inserted for clarity.

Claims 19, 24 and 59 have been amended to recite a *non-primate* embryo or animal.

Claims 25 and 62 have been amended by deleting reference to humans from the claim scope.

Claim 56 has been amended to recite the additional step of transferring the embryo to a surrogate female, for clarity.

Claim 66 has been clarified by insertion of a proviso that excludes the possibility of producing a primate embryo.

With respect to claims 18, and 60-61, these claims have been cancelled, and therefore this rejection is now moot.

The Applicant contends that the claims as amended are fully-enabled by the Specification, which teaches methods of nuclear transfer to produce non-primate embryos using suitable donor and recipient cells. While not restricting the donor or recipient cell type to a non-primate donor or recipient cell, the claims have been amended to include a proviso excluding the possibility of producing a non-primate embryo. The recipient cell has also been amended to recite an oocyte or a stem cell.

As the examiner is aware, nuclear transfer simply involves the removal of the nuclear DNA from one cell (termed the "recipient") which is replaced with the nuclear DNA of another cell (termed the "donor"). There is sufficient evidence from the literature to support the use of both oocyte and stem cell cytoplasm for use in nuclear transfer to generate either cloned animals or reprogrammed cell fate, respectively.

If the recipient is an oocyte, and the donor a somatic cell, then there is the potential to create a cloned embryo, after activation and embryo culture, and which if transferred to the reproductive tract may result in a cloned fetus and offspring. This is reproductive cloning and

the source of oocytes, activation and embryo culture methods to enable this are known by those skilled in the art.

However, if the recipient cell is from an existing embryonic stem (ES) cell line, and the donor is from a somatic cell, then the nuclear DNA in the somatic cell may be dedifferentiated (reprogrammed) in the resulting hybrid cell after nuclear transfer, under the influence of the embryonic stem cell cytoplasm. This process *does* involve nuclear transfer, but does not yield cells that are capable of forming an embryo or offspring on their own. Thus, these hybrid NT cells are not totipotent in their own right. Yet the hybrid cells may regain sufficient developmental plasticity, so that given the appropriate environmental cues, they may be directed along specific developmental paths to have utility in regenerative medicine if performed with human ES and somatic cells as recipients and donors, respectively.

Previous literature from 1997 demonstrates that pluripotent stem cell cytoplasm can be used to reprogram somatic cells, in the mouse *Tada et al.*, 1997. These hybrid cells contained both sets of nuclear DNA; one from the stem cell and the other from the somatic cell. In essence, this study confirms the origin of other forms of cytoplasm that could be used successfully in nuclear transfer. Thus, it is reasonable to expect that by taking a selected somatic donor cell in G1 of the cell cycle and fusing that to a stem cell cytoplasm would result in a proportion of successfully reprogrammed cells. Since the filing of the present application, this prediction has been substantiated further with experiments in mouse and humans, with potential benefit for regenerative medicine (*Tada et al.*, 2003; *Cowan et al.*, 2005).

Regarding methods that are directed to the cloning of a non-primate mammal, the recipient cell has been restricted to an enucleated oocyte. In addition, and as mentioned above, the relevant claims have been amended by referring to the step of transferring an embryo into a

surrogate of the same or a *closely related* species. A person skilled in the art would know that in order to produce a cloned mammal, the embryo would need to be gestated in a suitable uterine environment using a recipient (or surrogate) female from the same or closely related species, compatible with development. There are a number of examples in the art where recipient females from a closely-related species have been successfully used. A few such examples are provided below:

1. Cloned embryos produced using *Ovis orientalis musimon* donor nuclei transferred into domesticated sheep, *Ovis aries* (Loi *et al.*, 2001).
2. Cloned embryos produced using *Bos gaurus* donor nuclei transferred into *Bos taurus* domesticated cattle (Lanza *et al.*, 2000; Vogel, 2001).
3. Grant's zebra embryos transferred into domestic mares (Summers *et al.*, 1987).

Thus, Applicant believes that the pending claims are fully enabled and commensurate in scope with his contribution to the art, and respectfully requests that the rejection be withdrawn.

**2.6 REJECTION OF CLAIMS UNDER 35 U. S. C. § 112, 2<sup>ND</sup> PARAGRAPH, IS OVERCOME.**

*At pages 12 to 14 of the present Action, claims 2, 9, 13, 17, 23, 29-32, AND 59-62 were rejected under 35 U. S. C. § 112, 2<sup>nd</sup> paragraph, allegedly as being indefinite.*

Applicant respectfully traverses.

Without acquiescing in any way to the propriety of the rejection, and without comment on the merits of the rejection, in the interest of advancing certain claims of commercial importance to early allowance, Applicant has further clarified the language of these claims. Applicant notes that such amendments are in no way an indication of Applicant's acquiescence

to the Examiner's rejection, and expressly reserve the right to re-file claims directed to the original scope of the amended claims.

Claims 2, 9, 13, and 17 have been amended to improve the clarity of the language of the claim, and to properly provide the required antecedent basis for the dependent claims.

As claims 21, 23, 29, 30, 31, and 60-61 have been canceled; the rejection of these claims is now moot.

Applicant respectfully requests that the rejection now be withdrawn.

**2.7 THE REJECTIONS OF CLAIMS UNDER 35 U. S. C. § 102(b) ARE RENDERED MOOT.**

*At page 14, the Action rejected claims 20, 22, 23, 28, 29, and 33 under 35 U. S. C. §102(b) allegedly as being anticipated by McLaughlin et al. (Reprod. Fertil. Dev., 2:619-622 [1990], hereinafter "McLaughlin").*

Applicant respectfully traverses. However, in the interest of progressing certain aspects of the present case to allowance and mindful of patent term and economic issues of a protracted examination, Applicant has canceled the rejected claims. This cancellation is voluntary, and is done so without acquiescing to the propriety of the rejection in any way. Since the claims have been canceled, the rejection is now moot, and Applicant respectfully requests that it be withdrawn.

*At page 15, the Action rejected claims 20-23, 28-30, and 32-33 under 35 U. S. C. § 102(b) allegedly as being anticipated by Schnieke et al. (Science, 278:2130-2133 [1997], hereinafter "Schnieke").*

Again, Applicant respectfully traverses; however, as indicated above, Applicant has canceled the rejected claims, and the rejection is now moot. Applicant respectfully requests that the rejection be withdrawn.

*At page 16, the Action rejected claims 20-23, 28-33 under 35 U. S. C. § 102(b), allegedly as being anticipated by Bowen et al. (Biol. Reprod., 50:664-668 [1994], hereinafter "Bowen").*

Applicant again respectfully traverses the rejection; however, as indicated above, the rejected claims have been canceled, which renders the present rejection moot.

Applicant respectfully requests that this rejection under 35 U. S. C. § 102(b) also now be withdrawn.

## **2.8 THE REJECTIONS OF CLAIMS UNDER 35 U. S. C. § 103(a) ARE OVERCOME.**

*At pages 16-20 of the Action, the Office rejected claims 1, 2, 5-13, 16-33, 36, 39-43 under 35 U. S. C. § 103(a) allegedly as being unpatentable over Campbell et al. (PCT Intl. Pat. Appl. Publ. No. WO 97/07668 [6 March 1997], hereinafter "Campbell") in view of Boquest et al. (Biol. Reprod., 60:1013-1019 [1999], hereinafter, "Boquest"), and further in view of Alberts et al. (Mol. Biol. Cell, 3<sup>rd</sup> Ed., Garland Publishing, Inc. NY, pp. 903-904 [1994], hereinafter "Alberts").*

As to each rejection, the Applicant respectfully traverses.

Applicant notes for the record that a finding of obviousness under 35 U. S. C. § 103 requires a determination of the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed subject matter and the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of

ordinary skill in the art at the time the invention was made. *Graham v. John Deere Co.*, 148 USPQ 459 (U.S. S.Ct. 1966).

The relevant inquiry is whether the prior art suggests the invention and whether the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell*, 7 USPQ 2d 1673 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success *must be founded in the prior art* and not in the Applicant's disclosure (emphasis added) *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991).

Furthermore, in the case of *In re Dow Chemical Co.* (837 F. 2d 469, 5, U.S.P.Q.2d 1529, Fed. Cir. 1988) the court held that an "obvious-to-experiment" standard is not an acceptable alternative for obviousness, and that there must be a reason or suggestion in the art, *other than* the knowledge learned from the Applicant's disclosure.

Applicant also submits that the combination of references relied upon by the Examiner also clearly fails to satisfy the tripartite test of *In re O'Farrell* (7 U.S.P.Q.2d 1673, 1680, Fed. Cir. 1988). In *O'Farrell*, the Court held that in order for a single reference or a collection of references to obviate an invention, it must be shown that the reference(s) contain(s):

- (1) Detailed enabling methodology for practicing the claimed invention;
- (2) A suggestion for modifying the prior art to practice the claimed invention; and
- (3) Evidence suggesting that the invention would be successful.

For the cited combination of references to render the rejected and newly-presented claims legally obvious under 35 U. S. C. § 103, the references must provide one of ordinary skill in the art with a reasonable expectation of obtaining the results embodied by the pending claims.

Thus, Applicant respectfully disagrees with the Office's contention that the subject matter of the present claims is legally obvious in view of the art of record. Applicant believes that the

combination of references fails to meet the legal standard of *Vaech* or *O'Farrell*, and as such the rejections must be withdrawn.

In particular, the Applicant disagrees that the present claims are legally obvious in view of Campbell when taken together with Boquest and Alberts; and over Campbell in view of Boquest, Prather, Gadbois and Collas and provides the following reasoning to support his position that the rejections are improper:

First, while Campbell may claim methods of reconstituting an animal embryo by transferring a diploid nucleus in G0 or G1 phase into an enucleated oocyte, the reference certainly does not demonstrate the production of cloned embryos or animals with anything *other than* G0 donor cells. Indeed, prior literature using somatic cells for nuclear transfer had failed to generate cloned animals with any cells other than G0 donor cells. Thus, this reference is not enabling for G1 cells, and in fact, when taken together with the common general knowledge and prior art at the date of the invention, actually *teaches away from* the present invention.

The previous studies with G1 donors reported by Collas were limited to undifferentiated embryonic blastomeres and they did NOT use cultured differentiated (somatic) cells. It is only with the use of cultured differentiated cells that it is possible to clone an animal, as opposed to cloning an embryo. While early studies with undifferentiated embryonic blastomeres did indeed demonstrate that cells in G1 would avoid chromosomal errors following nuclear transfer with non-activated oocyte cytoplasm, it had not been demonstrated that differentiated somatic cells in G1 could be reprogrammed following nuclear transfer and yield viable cloned offspring. At the time, it was not at all obvious to the skilled artisan that such was possible.

It must be remembered that before the birth of "Dolly" the sheep in 1996 (the first animal to be cloned from an adult) no one had produced a cloned animal from a differentiated (*i.e.*, *somatic*) cell.

Moreover, it was considered at the time that the major reason for that success was the use of differentiated donor cells that had been forced to exit the cell cycle and had entered a so-called quiescent, or G0, state (*Wilmot et al.*, 1997). This view arose because from the pioneering cloning work in amphibians and in the mouse it was considered impossible to clone adult animals.

The criticality of the G0 donor cell state is reflected in a "News and Views" commentary that was published in the same issue of *Nature* as the *Wilmot et al* 1997 paper (*Stewart*, 1997). Colin Stewart states on line 3 of the legend for FIG. 1 that "their success is largely due to the fact that nuclei were taken from cells in the G0 phase of the cell cycle".

The reference by *Wilmot et al* also states on page 810, first paragraph, last sentence that "The birth of lambs from differentiated fetal and adult cells also reinforces previous speculation that by inducing donor cells to become quiescent it will be possible to obtain normal development from a wide variety of differentiated cells." Additionally they state on page 812, column one, last paragraph, lines 5-6 that "Our studies with cultured cells suggest that there is an advantage if cells are quiescent (ref 1, and this work)." Hitherto, the production of viable cloned mammals from differentiated somatic cells had not been demonstrated.

The Examiner is further reminded that earlier publications report the failure to generate viable cloned offspring from differentiated cells using unsynchronized cell populations or populations in which a large proportion of the cells would have been expected to be in G1. For example, *Collas and Barnes* in 1994 had, prior to *Wilmot et al* 1997, used bovine granulosa cells,

which possess a naturally long G1 phase, for nuclear transfer and failed to produce any cloned offspring from these somatic cells (*Collas and Barnes, 1994*). Similarly, unsynchronized sheep embryonic cells from late passage cultures, where a majority of the cells would be presumed to be in G1, also failed to result in cloned lambs (*Campbell et al., 1996*).

The fact that the first mammalian clones from differentiated cells were produced from G0 cells and previous attempts using G1 cells had failed, teaches away from believing that differentiated donor cells in G1 could be totipotent following nuclear transfer.

Given this, it was both surprising and unexpected from the studies reported in the present application that differentiated donor cells specifically selected in G1 of the donor cell cycle were indeed totipotent following nuclear transfer.

The present application also shows that with genetically modified fetal fibroblast donor cells, it was *even more surprising* that cloned embryos derived from G1 transgenic donor cells resulted in significantly greater rates of both development to term and the production of viable calves at weaning, compared to those cloned embryos derived from G0 donor cells (*Wells et al., 2003*). The present application includes an initial part of the data reported in *Wells et al 2003* (e.g., see Fig 5 of the Specification).

The Examiner takes the position that Boquest and Prather provide a mechanism to segregate G0 from G1 cells in a mixed population. Applicant asserts, however, that this distinction is arbitrary and the method requires the fixation of cells, which renders them non-viable and unable to be used successfully for nuclear transfer.

The Applicant asserts that neither Boquest nor Prather produces a pure population of cells at G1 stage of the cell cycle, nor any other cell cycle stage for that matter. They were only able to enrich for certain cell cycle stages but not select them for use in nuclear transfer. In addition,

the methods used by Boquest and Prather produced cells that had been fixed in ethanol and therefore cannot be used in nuclear transfer. Thus, the method could not be used to select populations of G1 cells for nuclear transfer.

Taking the results disclosed in Boquest and Prather at face value, there was an enrichment of G1 cells to around 80%, by examining small cells from cycling cultures (see *e.g.*, Prather, Table 2 and Boquest, Table 2). However, there are technique measurement factors that would make a person skilled in the art question these results.

The sorting methodology used in both Boquest and Prather relied on dual parameter flow cytometry, using simultaneous cellular DNA and protein content measures, in an effort to discriminate between different cell cycle phases within the cell population. The rationale is that as cells progress through the cell division cycle from G1, S, G2 and M phase, the DNA and protein content of the cell increases. G0 cells, that have exited the cell cycle, and G1 transient cells have the least protein and a 2C amount of DNA. However, there is no clear cut-off in protein or DNA content between cell cycle states as measured by flow cytometry. Especially in regard to protein content, it is a continuum (*e.g.*, see data in Boquest, FIG. 1; see also, Prather, FIG. 2) and artificial boundaries are established to characterize cell cycle states.

Boquest (and similarly, Prather) describes a visual method of discrimination of G0 from G1 by setting arbitrary gates (or boundaries) on a flow cytometer using a scatter-plot of green versus red fluorescence (see *e.g.*, paragraph 2 of column 1, p1014 and the results shown in panel 1 of FIG. 1, which combines protein and DNA measurements, respectively). No biological corroboration is provided for the G0/G1 cut-off point chosen, and the fact that it was a subjective estimate is acknowledged on page 1015, column 2, paragraph 1. In fact, the chosen protein cut-off point for the G0/G1 boundary is set at a much lower level (at approximately 200 units; see

FIG. 1) than the cut-off level (at approximately 400 units) with the serum-starved 2C cells (see *e.g.*, FIG. 2, panel 2 comparison of protein vs. DNA), which is the accepted method of producing G0 cells.

In addition, natural variation in DNA and protein content of cells within a given cell cycle stage (FIG. 1 and FIG. 2) combined with variation in the accuracy of measurement means that there will be significant error in this classification, given the continuum of data across the chosen boundary. The combination of all of these factors means that discrimination between different cell cycle stages in the sorting technique used must be considered arbitrary and will involve significant errors in the results obtained using this method. This is especially true in relation to setting the G0/G1 boundary. The Applicant, therefore, contends that the sub-population of cells claimed to be in G1 by the authors of Boquest and Prather did, in fact, also contain G0 cells.

This sorting inaccuracy is material because of the low efficiency levels of cloning using nuclear transfer, and the inability to attribute cloning success to G0 or G1 donor cells in impure, mixed cell populations. Thus, Boquest and Prather do not teach an accurate and reliable method of isolating a pure population of cells. Furthermore, neither Boquest nor Prather provided the means necessary for accurate discrimination between G0 and G1 phase cells. Likewise, the methods used by Boquest and Prather cannot be used in nuclear transfer to create a viable cloned embryo or animal, because each of those methods produces cells that have been fixed in ethanol.

Applicant respectfully requests therefore, that the rejection be withdrawn from all pending claims (Claims 18 and 61-62 have been canceled; thus the rejection of these claims is moot).

*At pages 20-23 of the Action, the Office rejected claims 1, 3, 4, and 64-66 under 35 U. S. C. § 103(a) allegedly as being obvious in view of Campbell together with Boquest, and further in view of Prather et al. (Cloning, 1(1):17-24 [March, 1999], hereinafter "Prather"), Gadbois et al. (Proc. Natl. Acad. Sci. USA, 89:8626-8630 [September, 1992], hereinafter "Gadbois") and Collas et al. (Biol. Reprod., 46:492-500 [1992], hereinafter "Collas").*

Applicant again respectfully traverses.

While Alberts suggests senescent cells exit the cell cycle in G0, this is contrary to other studies which state that G0 (quiescence) and senescence are distinct and that senescent cells arrest in late G1 of the cell cycle (Sherwood et al., 1998; Pignolo et al., 1998). Although a cultured fibroblast cell line *might* contain a sub-population of senescent cells arrested in G1, it had not been previously demonstrated that such cells could be used for nuclear transfer to generate cloned fetuses (see, e.g., the Specification at Example 7).

The kinase inhibitors used by Gadbois enriched the G1 population to 91%, but these cells could not be used for nuclear transfer following selection on a fluorescent activated cell sorter, as the flow cytometry method used cells fixed in ethanol. Moreover, Campbell fails to demonstrate that it is possible to clone an animal using G1 donor cells, and indeed, prior evidence taught away from this possibility. Although the suggestion for developing methods to arrest a high proportion of cells in G1 cells, *might* have been raised prior in 1999, such a population of G1 cells could not have been achieved using the teachings of Gadbois. Importantly, even if a population of viable G1 cells could have been obtained by some method, at the time of Gadbois' disclosure it was not at all obvious that G1 cells would result in successful somatic cell cloning.

Applicant believes that a skilled worker would not have been motivated to use a population of ethanol-fixed isolated cells after the teachings of Boquest, Prather, and Gadbois in the method of nuclear transfer identified by Campbell. Such a method, (whether the cell was isolated in G0 or G1), would clearly **not** result in the production of a viable nuclear transfer unit. Alternatively, if a skilled worker were to try and isolate and segregate a viable cell for nuclear transfer by following the teaching of Campbell, they would have been motivated to attempt isolation of a cell in G0 (and **NOT** a cell in G1).

Furthermore, Applicant has shown, for the first time that somatic cells isolated in the G1-phase of the cell cycle are totipotent following nuclear transfer, *i.e.*, G1 somatic cells can result in the birth of viable offspring. The present application describes for the first time a specific method that enables one to repeatedly isolate G1 donor cells at the time of nuclear transfer. This methodology was developed to ensure that each donor cell was indeed in the definitive G1-phase of the cell cycle. Importantly, Applicant's methodology has demonstrated for the first time that definitive G1 cells are totipotent. Only *after* considering the teachings of Applicant's present disclosure would one of skill in the art be motivated to predict that methods permitting the selective isolation of viable G1-phase cells would result in successful nuclear transfer.

In view of the combined literature cited by the examiner on this point, Applicant contends that it was not at all obvious at the date of the invention that a somatic cell in G1 could result in viable animals following NT. Prior work indicated that this was only possible with embryonic cells and not with somatic cells. The methods of flow cytometry did not allow the accurate segregation of an exclusive population of G1 donor cells that remained viable and useful for nuclear transfer.

The Applicant has also demonstrated that cloned animals produced by the method of the invention, (*i.e.*, from segregated G1 donor cells), had surprisingly better survival rates in both gestational and post-natal stages than for cloned animals produced from G0 cells. This represents a surprising and unexpected result in Applicant's development of the present methods. The result is certainly not what would have been expected from studying the prior art, which, as described above, clearly teaches away from the present invention's use of segregated G1 donor cells.

In summary, it is Applicant's position that the cited references (either alone, or in any combination) *cannot* render obvious the claimed invention, because the combination of references fails to provide both the required suggestion and the reasonable expectation of success of generating the claimed invention.

Therefore, because the claims in the instant application particularly point out distinctly claim novel, non-obvious, and useful methods, and further because each claim is clearly distinguished over the cited art, Applicant believes that, as a matter of fact, the rejection advanced under 35 U. S. C. § 103 cannot stand. Applicant respectfully submits that all aspects of the instant 35 U. S. C. § 103 rejections have been overcome and withdrawal of the rejections is earnestly solicited.

## **2.9 CONCLUSION**

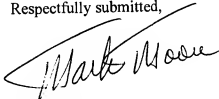
It is respectfully submitted that all claims are fully enabled by the Specification, that all pending claims are enabled, definite, and free of the cited prior art, and that the inventions embodied in those claims are useful, novel, and non-obvious. Applicant believes that the claims are acceptable under all sections of the Statutes and are now in condition for ready allowance.

Applicant earnestly solicits concurrence by the Examiner and the issuance of a Notice of Allowance in the case with all due speed.

Applicant notes for the record his explicit right to re-file claims to one or more aspects of the invention as originally claimed in one or more continuing application(s) retaining the priority claim from the present and parent cases.

Should the Examiner have any questions, a telephone call to the undersigned Applicant's representative would be appreciated, and in particularly in advance of any subsequent action on the merits.

Respectfully submitted,



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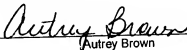
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Audrey Brown